PHARMACEUTICAL COMPOSITIONS OF NATEGLINIDE AND A HIGH AMOUNT OF A WATER-SOLUBLE FILLER

Technical Field of the Invention

The present invention relates to pharmaceutical compositions of nateglinide with 50-70% of water-soluble filler alone or in combination with a channeling agent.

Background of the Invention

Nateglinide is an amino acid derivative that lowers blood glucose levels by stimulating insulin secretion from the pancreas. It is widely indicated as monotherapy to lower blood glucose in patients with Type 2 diabetes. It is also indicated for use in combination with Metformin. Nateglinide oral tablets are commercially available in 60 mg and 120 mg strengths and are marketed by Novartis under the trade name STARLIX®.

The active agent nateglinide is described in EP 196222 and EP 526171. The active drug substance includes pharmaceutically acceptable acid addition salts, for example, sodium, maleate or hydrochloride. Nateglinide has a poor solubility and achieving the desired dissolution profile is difficult to achieve.

U.S. Patent No. 6,559,188 discloses particular pharmaceutical compositions of nateglinide. The pharmaceutical compositions disclosed include water-soluble lactose and water-insoluble microcrystalline cellulose as fillers. Lactose is present at a concentration of 34% to 36% w/w and microcrystalline cellulose is present at a concentration of 17% to 23% w/w, with the total concentration of filler (water-soluble and water-insoluble combined) ranging from 50-70% w/w.

Summary of the Invention

We have now surprisingly discovered that nateglinide tablets, when prepared with water-soluble filler alone at a concentration of 50-70% w/w, show a dissolution profile wherein at least 70% of the drug is released within 45 minutes. Further, we have also discovered that use of at least one channeling agent in the core along with the water-soluble filler improves dissolution.

In one general aspect there is provided an oral pharmaceutical composition that includes nateglinide or pharmaceutically acceptable salts thereof and a water-soluble filler at a concentration range of 50-70%w/w of the composition. The oral pharmaceutical composition may have a dissolution profile wherein at least 70% by weight of the

nateglinide is released within 45 minutes in 1000 ml, 0.01 N HCl, with 0.5% SLS (pH–1.2), using USP apparatus – II, at 50 rpm.

Embodiments of the pharmaceutical composition may include one or more of the following features. For example, the water-soluble filler may be one or more of lactose, white sugar, sucrose, glucose, sorbitol and mixtures thereof and in particular may be lactose.

The oral pharmaceutical composition may further include one or more pharmaceutically acceptable excipients. For example, the pharmaceutical composition may include one or more of binders, disintegrants, lubricants, and coloring and flavoring agents.

The binder may be one or more of methyl cellulose, hydroxypropyl cellulose, hydroxy propyl methyl cellulose, povidone, gelatin, gum Arabic, ethyl cellulose, polyvinyl alcohol, pullulan, pregelatinized starch, agar, tragacanth, sodium alginate, propylene glycol, and mixtures thereof. For example, the binder may be povidone.

The disintegrant may be one or more of starch, croscarmellose sodium, crospovidone, sodium starch glycolate, polacrillin potassium and mixtures thereof. For example, the disintegrant may be croscarmellose sodium.The lubricant may be one or more of colloidal anhydrous silica, stearic acid, magnesium stearate, calcium stearate, talc, hydrogenated castor oil, sucrose esters of fatty acids, microcrystalline wax, yellow beeswax, and white beeswax. For example, the lubricant may be magnesium stearate.

The oral pharmaceutical composition may be a tablet or capsule. The tablet may be coated with one or more functional and/or non-functional layers.

The oral pharmaceutical composition may further include one or more channeling agents. The channeling agent may be one or more of a sugar, a salt, a sugar alcohol, or combinations thereof. The sugar may be one or more of compressible sugar, glucose, and mannose. The salt may be one or more of sodium chloride and potassium chloride. The sugar alcohol may be one or more of mannitol, sorbitol, xylitol, erythritol, lactitol, and maltitol. For example, the channeling agent may be compressible sugar or it may be sodium chloride.

In another general aspect there is provided a process for preparation of an oral pharmaceutical composition of nateglinide. The process includes blending nateglinide, disintegrant, and a water-soluble filler to form a blend; granulating the blend with a binder

solution; drying and sizing the granules; and lubricating and compressing the lubricated granules to form an oral pharmaceutical composition. The water-soluble filler is present at a concentration of 50% to 70% w/w of the oral pharmaceutical composition.

The process may further include blending a channeling agent with the nateglinide, disintegrant, and water soluble filler to form a blend.

The granulation may be wet granulation or dry granulation.

The binder solution may include a binder and a solvent. The solvent may be one or more of methylene chloride, isopropyl alcohol, acetone, methanol, ethanol, and water.

Embodiments of the process for the preparation of an oral pharmaceutical composition may include one or more pharmaceutically acceptable excipients. The pharmaceutical excipients may be one or more of binders, disintegrants, lubricants, coloring and flavoring agents.

In another general aspect there is provided a method for the treatment of metabolic disorders, type 2 diabetes mellitus, or a disease or condition associated with diabetes mellitus. The method includes administering to a patient in need thereof a pharmaceutical composition of nateglinide. The pharmaceutical composition includes nateglinide or pharmaceutically acceptable salts thereof, and a water-soluble filler in a concentration range of 50-70%w/w of the composition.

The pharmaceutical composition administered may further include a channeling agent. The pharmaceutical composition administered may have a dissolution profile wherein at least 70% by weight of the nateglinide is released within 45 minutes in 1000 ml, 0.01 N HCl, with 0.5% SLS (pH–1.2), using USP apparatus – II, at 50 rpm.

Detailed Description of the Invention

The term 'nateglinide' as used herein includes nateglinide in a free or pharmaceutically acceptable acid addition salt, for example as a sodium or maleate salt. In particular, the composition includes the B- or H-type crystal modification of nateglinide, and in some particular embodiments the H-type. The active ingredient or a pharmaceutically acceptable salt thereof may also be used in the form of a hydrate or may include other solvents used for crystallization.

The dosage range of the nateglinide depends upon factors known to the person skilled in the art including body weight, age, the nature and severity of the condition to be

treated, and the mode of administration to be employed. Unless stated otherwise herein, nateglinide is preferably divided and administered one to four times per day.

Nateglinide can be administered in the dosage range of about 5 mg/day to about 1200 mg/day, for example about 10 mg/day to about 1000 mg/day or for example about 25 mg/day to about 800 mg/day.

'Channeling agents' as used herein include water-soluble excipients, which can be solubilized in water or gastrointestinal fluid, thus forming channels through which the water or the gastrointestinal fluid enters the formulation. This action aids in improving dissolution.

Suitable channeling agents include one or more of a sugar, for example compressible sugar, glucose, or mannose; a salt selected from sodium chloride, or potassium chloride; a sugar alcohol, for example mannitol, sorbitol, xylitol, erythritol, lactitol, or maltitol; or a mixture thereof.

The term 'other pharmaceutically acceptable excipient' refers to other inert ingredients of the composition, excluding the active drug substance. Suitable pharmaceutically acceptable excipients include one or more of fillers, binders, disintegrants, lubricants, glidants, and colors.

Suitable fillers include one or more of corn starch, lactose, white sugar, sucrose, glucose, sorbitol, calcium carbonate, calcium phosphate-dibasic, calcium phosphate-tribasic, calcium sulfate, microcrystalline cellulose, silicified microcrystalline cellulose, cellulose powdered, dextrates, dextrins, dextrose, fructose, kaolin, lactitol, mannitol, sorbitol, starch, and pregelatinized starch.

Suitable binders include one or more of methyl cellulose, hydroxypropyl cellulose, hydroxy propyl methyl cellulose, polyvinylpyrrolidone, gelatin, gum Arabic, ethyl cellulose, polyvinyl alcohol, pullulan, pregelatinized starch, agar, tragacanth, sodium alginate, and propylene glycol.

Suitable disintegrants include one or more of starch, croscarmellose sodium, crospovidone, polacrillin potassium, sodium and starch glycolate.

Suitable lubricants and glidants include one or more of colloidal anhydrous silica, stearic acid, magnesium stearate, calcium stearate, talc, hydrogenated castor oil, sucrose esters of fatty acids, microcrystalline wax, yellow beeswax, and white beeswax.

Suitable coloring agents include any FDA approved colors for oral use.

Nateglinide or a pharmaceutically acceptable salt thereof may be present in any amount which is sufficient to elicit a therapeutic effect and, where applicable, may be present either substantially in the form of one optically pure enantiomer or as a mixture, racemic or otherwise, of enantiomers.

Nateglinide may be present in an amount of about 5% to about 70% w/w, for example about 15% to about 40% w/w, based on the total weight of the dry composition.

Water-soluble filler may be present in an amount of about 50% to about 70% w/w by weight based on the total weight of the dry composition.

The channeling agents may be present in an amount of about 5% to about 30% w/w, for example about 10% to about 25% w/w, based on the total weight of the dry composition.

The solid dose formulation can be prepared by processes known in the art including one or more of wet granulation, dry granulation and direct compression and may be in the form of tablet or capsule.

The nateglinide tablet may be prepared by blending nateglinide and one or more water-soluble fillers, optionally a channeling agent, and disintegrant; granulating the blend with a binder solution; drying the granules; sizing; and lubricating and compressing the lubricated granules.

In another embodiment, nateglinide tablets may be prepared by blending nateglinide, water-soluble filler, optionally a channeling agent, disintegrant and binder; granulating the blend with a solvent; drying the granules; sizing; and lubricating and compressing the lubricated granules.

Granulation may be carried out in fluidized bed dryer and sizing can be done by milling or pulverization.

In another embodiment, the nateglinide tablet may be prepared by blending nateglinide, water-soluble filler, optionally a channeling agent, disintegrant and binder; compacting or slugging the blend; breaking the slugs to make granules; and lubricating and compressing the lubricated granules.

In yet another embodiment the nateglinide tablet may be prepared by blending nateglinide, water-soluble filler, optionally a channeling agent, disintegrant, binder and lubricant; and compressing.

The tablets prepared by the present invention may be coated with one or more additional layers including film-forming agents and/or pharmaceutically acceptable excipients.

The coating layers over the tablet may be applied as a solution/dispersion of coating ingredients using any conventional technique known in the prior art including spray coating in a conventional coating pan or fluidized bed processor, and dip coating.

Suitable solvents used for preparing a solution/dispersion of the coating ingredients include one or more of methylene chloride, isopropyl alcohol, acetone, methanol, ethanol, water and the like, and mixtures thereof.

Suitable film forming agents include one or more of ethyl cellulose, hydroxypropyl methylcellulose, hydroxypropyl cellulose, methyl cellulose, carboxymethylcellulose, hydroxymethylcellulose, hydroxyethylcellulose, hydroxypropyl methyl phthalate, cellulose acetate, cellulose acetate trimelliatate, cellulose acetate phthalate; waxes such as polyethylene glycol; methacrylic acid polymers such as Eudragit ® RL and RS; and the like and mixture thereof. Alternatively, commercially available coating compositions comprising film-forming polymers marketed under various trade names, for example Opadry® may also be used for coating.

The following examples further exemplify the invention and do not limit the scope of the invention.

EXAMPLE 1

INGREDIENTS	QUANTITY (WT/TABLET) MG
Intragranular Ingredients	
Nateglinide	121.21*
Lactose	424.16
Povidone	12
Croscarmellose sodium	20
Colloidal silicon dioxide	16
Purified water	q.s
Extragranular Ingredients	
Croscarmellose Sodium	12.8
Colloidal silicon dioxide	12.8
Magnesium stearate	11.4

** Equivalent to Nateglinide 120mg after potency and moisture adjustment*

PROCEDURE:

1. Nateglinide along with lactose, povidone, colloidal silicon dioxide and croscarmellose sodium are mixed in a high shear mixer and granulated using purified water.
2. The wet granules are dried in a fluid bed drier, passed through a screen and then subjected to sizing.
3. The extragranular colloidal silicon dioxide and croscarmellose sodium are mixed, passed through a screen and blended with the granules of step 2.
4. The magnesium stearate is passed through a screen, blended with the blend of step 3 and the total mixture is compressed to tablets.

EXAMPLE 2

INGREDIENTS	QUANTITY (WT/TABLET) MG
Intragranular Ingredients	
Nateglinide	121.21*
Lactose	343.79
Sodium chloride	80
Povidone	12
Croscarmellose sodium	20
Colloidal silicon dioxide	16
Purified water	q.s
Extragranular Ingredients	
Croscarmellose Sodium	12.8
Colloidal silicon dioxide	12.8
Magnesium stearate	11.4

** Equivalent to Nateglinide 120mg after potency and moisture adjustment*

PROCEDURE:

1. Nateglinide along with lactose, sodium chloride, povidone, colloidal silicon dioxide and croscarmellose sodium are mixed in a high shear mixer and granulated using purified water.
2. The wet granules are dried in a fluid bed drier, passed through a screen and then subjected to sizing.
3. The extragranular colloidal silicon dioxide and croscarmellose sodium are mixed, passed through a screen and blended with the granules of step 2.
4. The magnesium stearate is passed through a screen, blended with the blend of step

3 and the total mixture is compressed to tablets.

EXAMPLE 3

INGREDIENTS	QUANTITY (WT/TABLET) MG
Intragranular Ingredients	
Nateglinide	121.21*
Lactose	343.79
Compressible sugar	100
Povidone	12
Croscarmellose sodium	20
Colloidal silicon dioxide	16
Purified water	q.s
Extragranular Ingredients	
Croscarmellose Sodium	12.8
Colloidal silicon dioxide	12.8
Magnesium stearate	11.4

** Equivalent to Nateglinide 120mg after potency and moisture adjustment*

PROCEDURE:

1. Nateglinide along with lactose, compressible sugar, povidone, colloidal silicon dioxide and croscarmellose sodium are mixed in a high shear mixer and granulated using purified water.
2. The wet granules are dried in a fluid bed drier, passed through a screen and then subjected to sizing.
3. The extragranular colloidal silicon dioxide and croscarmellose sodium are mixed,

passed through a screen and blended with the granules of step 2.

4. The magnesium stearate is passed through a screen, blended with the blend of step and the total mixture is compressed to tablets.

***In vitro* dissolution study**

The *in vitro* release profiles of nateglinide from the tablets of Examples 1 to 3 were studied in 1000 ml, 0.01 N HCl, with 0.5% SLS (pH–1.2), using USP apparatus – II, at 50 rpm.

Table 1: In vitro release of nateglinide from tablets

Time	Cumulative percentage (%) release of nateglinide from Tablets			
	STARLIX	Example 1	Example 2	Example 3
10	62	40	62	66
20	-	43	-	-
30	65	72	76	80
45	67	77	83	87
60	72	-	-	-
Infinity	93	96	96	96

Table 1 indicates that compositions containing water-soluble filler alone (Example 1), or in combination with a channeling agent (Example 2 and 3) show a dissolution profile comparable to STARLIX®.

While several particular forms of the invention have been illustrated and described, it will be apparent that various modifications and combinations of the invention detailed in the text can be made without departing from the spirit and scope of the invention.